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(54) Title: AGGLUTINATION BASED SAMPLE TESTING DEVICE

(57) Abstract: A sample testing device (100) for testing for the presence of a component of interest in a liquid sample comprises: (a) at least one capillary pathway (120) which has an upstream end and a downstream end and which incorporates a reagent system capable of causing agglutination with said component to be detected (the test capillary); (b) preferably, but optionally, at least one capillary pathway (121) having an upstream end and a downstream end (the control capillary); (c) a sampling region (114) to which the liquid sample is applied and from which the sample is able to enter the upstream ends of the test capillary(s) (120) and if present the control capillary(s) (121); (d) a power source (108, 109); (e) detection arrangements (117, 118) electrically associated with said power source (108, 109) for detecting the presence of liquid at a downstream region of said testing capillary(s) (120) and if present the control capillary(s) (121); (f) display means (113) operated by said power source (108, 109) for indicating the result of the test; and (g) signal processing means (112) associated with the power source (108, 109), detection arrangement (117, 118) and display means (113) for evaluating the result of the test and providing said result on the display means. The device may be used for a pregnancy test, more particularly for determining the presence of hCG in urine.

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analyte within the indicator zone so that the amount of label at the indicator zone builds up to give a visible colour change. The presence of this immobilising agent may provide a slight amount of colour to the indicator region and it is this colour that is intensified when a positive result is observed. For example, the strip at the indicator region may be pale blue. When the test has been used and the analyte has bound a labelled antibody, which is immobilised at the indictor region, the strip at the indicator region may be a darker blue. The colour change is not easily reproducible or accurately readable by eye, especially under varying light conditions

Furthermore, in tests which require reading a colour change by eye, a user of an analyte assay device may have a preferred outcome to the assay in mind when reading the assay results and this may cloud their interpretation of the colour change. For example, a user of a pregnancy test kit (such as based on an antigen/antibody binding reaction for the detection of hCG) which indicates pregnancy by an intensification of the colour at the indicator region may see an intensification in colour more readily if they wanted to be pregnant than if they did not want to be pregnant. This leads to error in determining the presence of the analyte and the condition which is associated with the presence of that analyte, in this case pregnancy.

Another factor can arise from the test continuing to run after the initial result is given. The test is optimised to give a result in a short time frame, 1-3 minutes. However the antibody-antigen binding reaction continues to occur as long as the test strip is wet and analyte can flow. Since every sample of female urine will contain a basal level of hCG, it is possible that over time sufficient colour can build up to be detectable

In order to overcome the above disadvantages, electrochemical detection has been proposed for pregnancy testing devices. Thus, for example, WO-A-00 00827 (Moorlodge Biotech Ventures Limited) discloses a device in which a specific binding partner for the analyte has a label which is directly or indirectly electrochemically detectable, the device further comprising an electrochemical detection arrangement. The electrochemically detectable label may, for example, be a P1 nuclease label, in

By way of further background to the present invention, reference is also made to WO-A-99 35497 (Bio-Diagnotics Limited) which discloses a device for testing liquids. The device specifically disclosed in WO-A-99 35497 is for identifying blood groups and comprises a co-operating plate and lid arrangement which together define a number of capillary channels, each having an upstream end into which blood to be tested is introduced and a downstream vent (to allow blood flow along the capillaries). The device incorporates three capillary channels which, part way along their lengths, are formed into one or other of the 'indicator letters' A, B or O (i.e. blood group designations). Upstream of the indicator letters, each capillary channel has an agglutination reagent system that will cause agglutination of blood which is of a type represented by the indicator letter of that channel. Thus, for example, the channel formed with 'A' as the 'indicator letter' incorporates an agglutination reagent system that will cause agglutination of blood type A (but not types B or O). There is a further capillary track (along which blood may travel) which does not include an agglutination system and which has a 'check mark' instead of an 'indicator letter'. Apart from the 'indicator letters' and the 'check mark' (all of which are initially colourless) the device otherwise has a red background.

To determine blood group type, a blood sample is introduced at the upstream ends of the capillary tracks. Blood should flow unhindered along the track associated with the 'check mark' which will then become coloured red as an indication that the device is functioning properly. This track can therefore be considered as a 'control track'.

Depending on the blood type of the sample under test, the blood will become agglutinated in one of the other three tracks but will flow along the other two. Thus, for example, if the blood group is of the type A then the blood will become agglutinated in the track having the 'A' as the 'indicator letter'. Blood in this track is therefore not able to reach the 'indicator letter'. In contrast, blood is able to flow fully along the other two tracks and fill the 'indicator letters' associated therewith.

The device of the invention, which is preferably constructed as a hand-held device, is useful for the rapid analysis of samples (generally a liquid sample) to detect the presence (or otherwise) therein of a component of interest (also referred to herein as the anlayte) and provide, on the display means, a read-out of the test result. As described more fully below, a particular embodiment of the invention is a pregnancy testing device which is capable of analysis for the presence (or otherwise) in urine of a hormone (e.g. human Chorionic Gonadotropin) which is associated with pregnancy. The invention is not however limited to pregnancy testing devices and many other analysis formats are possible.

Devices in accordance with the invention may be constructed as single use devices which may be employed for carrying out a single assay and then disposed of.

The or each capillary pathway is preferably in the form of a capillary tube. It is however also possible for the capillary pathways to be formed in a chromatographic or other membrane, e.g. of nitrocellulose. Further possibility is for the or each capiliary pathway to be formed of porous or fibre material (e.g. the pathway is formed in a hollow fibre).

The device of the invention incorporates one or more capillary pathways each of which is associated with a detection arrangement for detecting the presence (or otherwise) of liquid at a downstream region of the respective pathway. One of these pathways, i.e. that designated as (a) above, is a 'testing' pathway and the other, i.e. that designated as (b) above (if present) is a 'control' pathway'. The control pathway if present is such that liquid introduced into the upstream end thereof is capable of flowing, under capillary action, at least as far as the detection arrangement associated with that pathway. This provides a signal to the signal processing means confirming that liquid has travelled to the required extent along the control pathway. This, in effect, confirms that the device is functioning normally. The 'testing pathway' is also such that liquid sample introduced into its upstream end is (at least initially) capable of flowing by capillary action along the 'testing pathway'. However the testing

sample or is not present above a predetermined amount, as appropriate) and an appropriate message can be shown on the display device. Alternatively if liquid has not reached the detection arrangement associated with the testing pathway within a specified time or at all, then the result of the test is 'positive' and once again an appropriate message is displayed (if liquid did not reach the detection arrangement associated with the control pathway then a message such as Test Void would be displayed).

The agglutination system will be selected depending on the component to be detected in the sample. The agglutination system may however comprise a binding partner (for example, in certain cases, an antibody) for the component. The agglutination system most preferably comprises particles (e.g. latex beads having a size of 300 nm to 10 μm, depending upon the size and concentration of the target analyte - in the case of hCG particle sizes of 1 - 10 μm are preferred) on which the binding partners are immobilised. Alternatively or additionally binding partners may be immobilised on the walls of the capillary.

For agglutination to occur each molecule of analyte must be capable of binding two or more particles. In the case where the analyte is hCG, the particles may be provided with binding partners specific for the two chains on the hCG molecule (i.e. one against the alpha chain and one against the beta chain. The purpose of a dual epitope system is spatially to separate the binding events so that they are in different parts of the analyte molecule. This gives greater reliability of forming an agglutination complex in low analyte numbers.

The agglutination system utilises two physical principles to slow the flow rate and block the capillary pathway. In the optimal design, the agglutination reaction occurs rapidly and a plug is formed, which creates a dam, blocking flow of liquid. Alternatively, the agglutination complexes form a drag on the flow of the liquid and act as a counter force to the forward draw of capillary pressure. When the draw equals the forward force, the liquid front runs out of energy and flow stops. The choice of mechanism will depend upon the kinetics of the binding reaction and the speed of

The agglutination reagent system will generally be specific for the analyte to be determined. A wide range of agglutination reagent systems are however known to those skilled in the art and individual sampling devices may readily be constructed for a correspondingly wide range of analytes. A device in accordance with the invention may for example be constructed for detecting a specific peptide hormone in a liquid sample. Alternatively a device may be constructed for determining a particular bacteria or virus as the analyte. For all of these possibilities, the agglutination reagent system may comprise an antibody (or antibodies) for the analyte. It is possible, for example, for the device to include a reagent system comprising two different 'types' of antibody, one of which recognises a first epitope on the analyte and the other of which recognises a second epitope. A portion of the antibodies may be immobilised on latex beads and the remainder may be immobilised on the inner walls of the capillary of the test pathway.

In order to enhance sensitivity of the device (e.g. to enhance the change in flow rate) it is possible for the test capillary to incorporate a particulate material that will effectively change the dimensions of the capillary. Examples of such particulate materials are inert materials such as silica and bentonite Alternatively the particulate material may be a swellable polymer such as Sephadex G100 or G50. The particulate material may be admixed with the agglutination reagent system or laid down separately in the test capillary, generally downstream of the agglutination reagent system.

It should be appreciated that the control pathway (if present) may incorporate the same material as the test pathway, except the "agent" that effects agglutination. Thus for example if the agglutination reagent system comprises latex beads with antibody bound thereto then the control pathway may also incorporate latex beads but without antibody. Similarly any particulate material as described above (e.g. silica, bentonite or Sephadex) that is present in the test pathway may also be present in the control pathway, ideally in a similar way (e.g. admixed with latex beads).

The device incorporates signal processing means that are operatively linked to the display device and the liquid detection arrangements associated with the capillary pathway(s). These detection means may for example comprise pairs of electrodes, each such pair being within (or being associated with) each or any of the capillary pathways at or towards the downstream end thereof. For the purposes of detecting liquid, a potential difference is applied across the electrodes of each pair. Liquid that has reached any one pair of electrodes will allow a current to flow across that pair of electrodes and this will be detected by the signal processing means for the purposes of evaluating the result of the test.

A detection arrangement comprised of such electrodes is particularly suitable where the liquid is conductive *per se* if the liquid is not conductive then (solid) electrolyte may be deposited in the capillary pathway(s) upstream of the detection electrodes so that (with the dissolved electrolyte) the liquid has become conductive by the time it reaches the electrodes.

Alternatively the detector may be an optical detector. For example, the detector may comprise a reflectometer. For the purposes of optical detection, a dye or dyed particles may be laid down in the capillary pathway(s) upstream of the detector. Liquid passing through the portion of the pathway(s) having the dye or dyed particles becomes coloured for the purpose of optical detection.

The signal processing means may incorporate a timer that is activated at the start of the test. In this case, the test is conducted for a predetermined period of time to determine whether or not the liquid reaches the detection arrangements associated with the testing pathway within that time. This caters for the possibility that, for a 'positive' test, the agglutination reagent system does not completely stop liquid flow but prevents it reaching the detection arrangement (associated with the testing pathway within a predetermined time). Alternatively the timing may be activated at a point part way along the track, e.g. half way along the capillary track.

A top plate of the same material as the base may subsequently be applied by, for example, ultrasonic welding to complete the capillary arrangement.

The exemplary device incorporates an upstream sample receiving chamber and a downstream detection arrangement of the type outlined above. The chamber may (but not necessarily) incorporate a pad which provides the advantage of minimising spilling or splashing during sample testing. The pad may be of a fibrous material, e.g. cellulose, and a variety of materials are available commercially from suppliers such as Filtrona or Porex. Fibrous pads may exert a counter capillary force to the capillary channel and the selection of pad material will depend on the dimensions of the capillary channel since these determine the capillary force. A suitable pad material for the 500 μm triangular capillary channel is available from Filtrona under the code R22087.

Incorporated in the test capillary is an agglutination reagent system comprised of particles with immobilised antibody to hCG. In general, the larger the capillary channel the larger the diameter the particles needs to be. A suitable particle size for the 500 micron triangular capillary is 5 microns. Examples of suitable particles include 5 μm polystyrene spheres from Polymer Laboratories.

The agglutination reagent system may be mixed with Sephadex G100 to produce a slurry comprised (w/v) 0.08-10% latex particles and 0.08-5% Sephadex. 1.6 μL of the mixture may be deposited over the first centimetre of the test capillary and dried by incubation at room temperature. This provides a plug which focuses the agglutination reaction and also provides a swelling material to help trap small agglutination complexes.

A similar slurry (but in which the latex beads do not incorporate the antibody to hCG) may be laid down and dried in the control capillary.

The top plate may now be applied by ultrasonic welding and the assembly stored with dessicant.

source 9. Each pair of electrodes 5 and 6 is associated with the chip 7 for the purpose to be described.

Capillary pathway 2 is referred to as the 'control track' and capillary pathway 3 as the 'test track '.

Provided in test track 3 already mentioned in detail above is an agglutination reagent system comprised of latex beads 10 (see Fig. 2), e.g. having a diameter of 3-5 μm, on which anti-hCG antibody is immobilised. Additionally provided in the test track 3 downstream of the beads 10 is anti-hCG antibody immobilised on the inner walls of the test track 3.

There is no agglutination reagent system in control track 2.

An additional feature of the test track 3 is a weir 11, the purpose of which again will be described later.

As described above, each pair of electrodes 5 and 6 is associated with the logic circuit 7. The pairs of electrodes 5 and 6 serve, in effect, to detect the presence or otherwise (as represented by boxes 12 and 13) of liquid towards the downstream end of the capillary pathway 2 or 3 as appropriate. More particularly, a potential difference is applied across each of the electrode pairs 5 and 6. The presence of urine between the electrodes of electrode pair 5 will mean that a current can pass between the electrodes 5 and be detected by the logic circuit 7. Similarly the logic circuit 7 is able to detect the presence of liquid (urine) at the downstream ends of capillary pathway 3.

The illustrated power source 9 may be a 'permanent source' e.g. a battery. Alternatively it may be a solar cell which generated power only when the device is removed from, say, a light opaque housing. A further possibility, which is preferred in accordance with the invention, is that the power source 9 comprises dissimilar metals arranged to generate a current by virtue of the presence of urine on the pad 4.

The logic circuit 7 detects whether liquid has reached one, other or both of electrode pairs 5 and 6 and provides a display on the LCD device in associated with the 'pattern' of liquid detected (or not detected) at the electrode pairs 5 and 6. The possibilities for all such 'patterns' are summarised in the following table where 'YES' indicates that liquid has been detected and 'NO' indicates that liquid has not been detected.

ELECTRODE PAIR 5	YES	YES	NO	NO
ELECTRODE PAIR 6	YES	NO	NO	YES
RESULT	NOT PREGNANT	PREGNANT	DEVICE MALFUNCTION	DEVICE MALFUNCTION

It will be appreciated that an appropriate message is then displayed on the LCD device 8.

Reference is now made to Fig 3 which illustrates a practical embodiment of pregnancy testing device 100 in accordance with the invention.

The device 100 comprises upper and lower elongate casing components 101 and 102 respectively which, in the assembled device, are securely clipped or sealed together.

In use, the device 100 is held at its right hand end (as viewed in Fig 3) at which the casing components are provided with dimples affording 103 finger-grip formations. At the end of the device remote from the dimples 103, the upper casing component 101 is provided with an elongate aperture 104 (extending transversely to the length of the upper casing component 101) providing a sampling window.

device (by means of studs) such that one of its width wise edges abuts against the absorbent pad 114. Each channel 120 and 121 extends from (and opens out at) the width wise edge of the plate 119 abutting the pad towards the opposite end of the plate before turning back through 180° and subsequently turning through 90° to open out at a longitudinal edge of the plate.

Apertures (not shown) are provided in the 'floor' of each channel 120 and 121 where it turns through 90° to reach the longitudinal edge of the plate. With the plate located in position in the PCB board the aforementioned apertures locate one above each of the electrode pairs 117 and 118..

The plate 119 is associated with a lid 123 which cooperates with the plate to form capillary pathways from the channels 120 and 121.

One of the pathways is a control pathway and thus corresponds, in principle, exactly with the control track 2 described above with reference to Fig 1. The other capillary pathway is a test track and therefore corresponds in principle with test track 3 described above with reference to Fig 1. Each lane may incorporate two weirs positioned equidistant from each other and from the ends of the respective lane.

In use of the device 100, urine to be tested is applied to the absorbent pad via the aperture 104. As the pad wets, the urine comes into contact with the interdigitated combs 108 and 109 so that a current is generated. This current serves to operate the logic circuit 112 and, in effect, switches the device 'on'. Additionally, liquid from the pad enters the upstream ends of the two capillary pathways. Given that the device is working properly then urine passes along the control pathway 120 until it reaches the aperture in the track at , at which point at least a portion of the urine from the control pathway 'drops' onto the pcb. The presence of urine on the pcb is detected by the logic circuit in view of the fact that a current can now pass between the electrode pair at 117. As previously mentioned an absorbent material placed over the electrodes at 117 will facilitate liquid transfer.

CLAIMS

1. A sample testing device for testing for the presence of a component of interest in a liquid sample, the device comprising:

(a) at least one capillary pathway which has an upstream end and a downstream end and which incorporates a reagent system capable of causing agglutination with said component to be detected (the test capillary);

(b) preferably, but optionally, at least one capillary pathway having an upstream end and a downstream end (the control capillary);

(c) a sampling region to which the liquid sample is applied and from which the sample is able to enter the upstream ends of the test capillary(s) and if present the control capillary(s);

(d) a power source;

(e) detection arrangements electrically associated with said power source for detecting the presence of liquid at a downstream region of said testing capillary(s) and if present the control capillary(s);

(f) display means operated by said power source for indicating the result of the test; and

(g) signal processing means associated with the power source, detection arrangement and display means for evaluating the result of the test and providing said result on the display means.

2. A device as claimed in claim 1, wherein the power source comprises electrodes of dissimilar metals provided at the sampling region of the device, said electrodes being adapted to generate a current when liquid sample is applied to said region.

11. A device as claimed in claim 10, wherein downstream regions of the or each capillary pathways have apertures and the or each detection arrangement is provided beneath a said aperture.

12. A device as claimed in any one of claims 1 to 11 wherein the or each capillary pathway is a capillary tube.

13. A device as claimed in any one of claims 1 to 9 wherein the or each capillary pathway is formed in a chromatographic or other membrane.

14. A device as claimed in any one of claims 1 to 9 wherein the or each capillary pathway is formed of porous or fibre material.

15. A device as claimed in any one of claims 1 to 14, wherein the or each detection arrangement comprises a pair of electrodes across which a potential difference may be applied.

16. A device as claimed in any one of claims 1 to 15 wherein the test capillary incorporates a particulate material to enhance the change in flow rate.

17. A device as claimed in claim 16 wherein said material is an inert particulate material.

18. A device as claimed in claim 17 wherein said inert particulate material is silica or bentonite.

19. A device as claimed in claim 16 wherein said material is a swellable polymer.

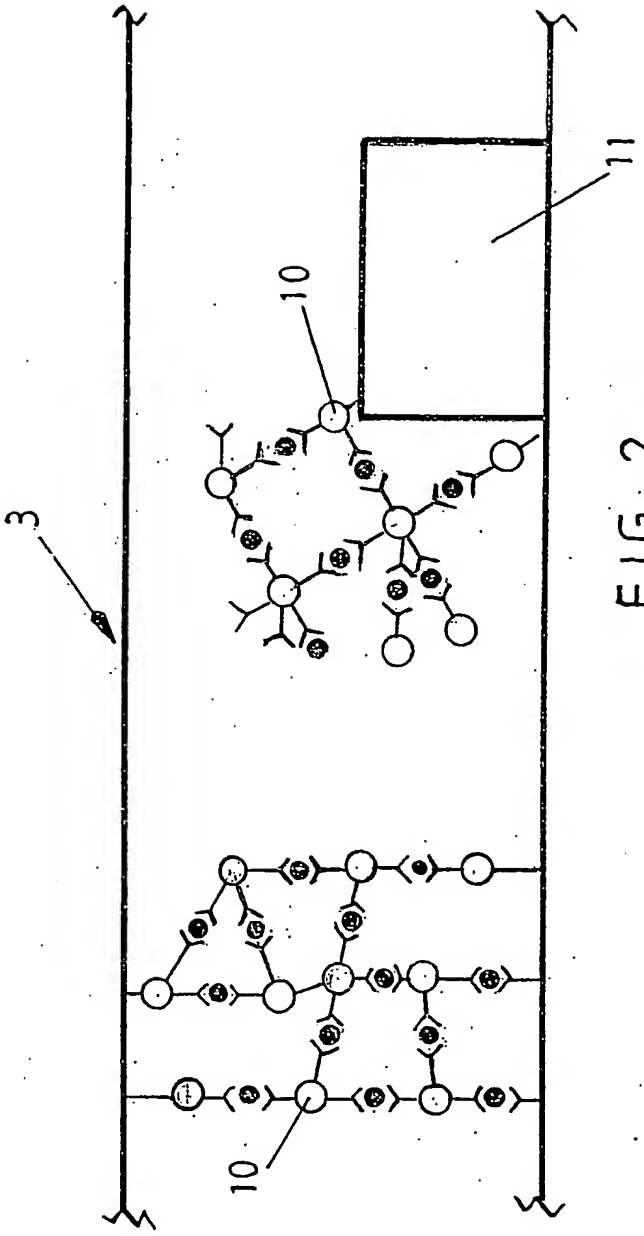

FIG. 2

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/53 G01N33/543 G01N33/76

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, INSPEC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents:

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Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
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